

A Randomized Study of Mitomycin-C Application in the
Endoscopic Treatment of Patients with Laryngotracheal Stenosis

IRB Study: 11-07508
IRB Approval: 12/27/2018
NCT: 01523275

A. Specific Aim

Obstruction of the upper airway caused by laryngotracheal stenosis (LTS) often results in severe morbidity and even mortality. Treatment of LTS continues to present a challenge and a wide array of surgical techniques have been employed. Despite multiple endoscopic and/or open reconstructive procedures, patients often experience restenosis as a result of the abnormal wound-healing process that initially instigated the airway obstruction^{1,2}. The high rate of stenosis relapse has therefore motivated researchers to find new methods to modulate and control the wound-healing process of the airway. Although other adjuvant treatments such as steroids and antibiotics have been investigated in LTS³⁻⁵, much attention in recent years has turned to the use of topical mitomycin-C (MMC).

As a topical application, MMC has been shown to inhibit fibroblast proliferation in wound-healing processes⁸ and is now routinely used in the endoscopic management of LTS. In order to relieve the airway stenosis and immediately increase the airway diameter, patients undergo microdirect laryngoscopy or tracheoscopy with placement of relaxing radial incisions and mechanical balloon dilation. Topical MMC is placed in the incisions with the intent to prevent or reduce the rate of restenosis. However, despite numerous animal and human studies¹¹⁻¹⁴, the benefit of MMC in LTS patients remains questionable.

The goal of this research is to improve our understanding of LTS treatment by directly evaluating the effect of MMC as an adjunctive therapy to standard endoscopic surgical management of LTS. We propose a prospective, randomized, double-blinded, placebo-controlled study to assess the efficacy of MMC as an adjuvant therapy in the treatment of LTS. A cohort of 60 LTS patients will be enrolled with the goal sample size set at 44 subjects. Subjects will be randomized into a MMC group or a placebo group. All subjects will undergo standard endoscopic surgical treatment for their LTS. Subjects in the MMC group will then undergo topical application of MMC placed into their incisions, while the placebo group will undergo saline application. We propose the following specific aim and hypotheses:

Aim: To assess the efficacy of topical MMC as an adjunctive therapy to endoscopic surgical treatment in LTS patients.

The primary outcome measure will be the interval to repeat surgical intervention. Secondary outcome measures will be the change in patient reported symptom scores, duration of symptom improvement, and peak inspiratory flow measurements.

Analysis 1: To determine changes seen with topical MMC therapy

Hypothesis 1a: MMC group patients will have longer intervals to repeat surgery than the placebo group.

Hypothesis 1b: MMC group patients and placebo group patients will have similar improvements in symptoms after surgical treatment for LTS.

Hypothesis 1c: MMC group patients will have longer durations of symptom improvement when compared to placebo patients.

Hypothesis 1d: MMC group patients and placebo group patients will have similar improvements in peak inspiratory flow measurements after surgical treatment for LTS.

Analysis 2: To evaluate the association between patients' subjective symptoms and pulmonary function testing measurements.

Hypothesis 1a: There will be an association between patient reported symptoms and peak inspiratory flow measures.

B. Background and Significance

B.1 Etiology of LTS and patient selection for endoscopic surgical management

LTS in the current era is most commonly caused by mechanical trauma from prolonged intubation or tracheotomy. Other etiologies include respiratory infections, external trauma, or inflammatory rheumatological disease, such as Wegener's granulomatosis. In many patients, no specific etiology is found and they are diagnosed with idiopathic LTS. Multiple studies have demonstrated an association between laryngopharyngeal reflux and LTS regardless of etiology and LPR may be implicated as the primary etiology in some cases. An important consideration in the management of LTS is determining the degree of cartilage involvement. In a study published by Simpson et al., it was demonstrated that endoscopic management of LTS was most successful in stenoses that were not completely circumferential, less than 1.0cm in vertical height, and not associated with significant cartilaginous involvement. Based on this early study and subsequent experience, LTS with cartilaginous involvement is not typically considered to be amenable to endoscopic surgical management with radial incisions and dilation.

B.2 Mitomycin-C is routinely used as an adjunctive therapy in the treatment of LTS with the intent to prevent scar reformation. Discovered in 1956, MMC is an antimicrobial agent which has antimetabolite and antiproliferative properties⁶. It is produced by *Streptomyces caespitosus* and acts as an alkylating agent to inhibit DNA synthesis⁷. As a topical application, MMC has been shown to inhibit fibroblast proliferation in wound-healing processes⁸. The first clinical use of topical MMC occurred in 1963 by ophthalmologists to reduce scar tissue formation in pterygium surgery with remarkable results⁹. The use of MMC in the treatment of airway stenosis was first reported in 1998¹⁰ and is now routinely used in the endoscopic management of LTS.

B.3 The proposed research will provide prospective, randomized controlled data regarding the efficacy of MMC as an adjunctive therapy in the endoscopic surgical treatment of LTS. With two exceptions, published clinical studies of MMC in LTS have been retrospective case series or cohort studies. Most report positive outcomes, supporting the use of MMC as an adjuvant treatment^{15,16}. Yet, in a prospective, randomized control trial of MMC in pediatric patients after open laryngotracheal reconstruction, outcomes were identical between the group who received MMC and the saline placebo group¹⁷. The second exception is a randomized, prospective, double-blind, placebo controlled trial that examined the efficacy of two topical application of MMC

given 3-6 weeks apart compared to a single topical application in endoscopic treatment of LTS¹⁸. Although the results suggest that two applications reduced the restenosis rate for 2 to 3 years, relapse rates at 5 years were the same between the two groups. A recent literature review on the use of topical MMD as an adjunctive in airway surgery concluded that “heterogeneity within the clinic studies, the lack of controlled data, and the lack of significance in the pooled animal data suggest that the utility of MMC is still undetermined”¹⁹.

B.4 Measures of LTS treatment

Interval to repeat surgery: Endoscopic treatment of LTS with radial incisions and dilation results in significant improvement in the patient’s symptoms. However, the short-term improvement is often associated with long-term relapse. Studies have reported a 40-70% recurrence rate over months to years (Simpson GT, *Ann Otol Rhinol Laryngol* 1982; 91:384-388., Duncavage JA *Ann Otol Rhinol Laryngol* 1985; 94:565-569, Ossoff RH, *Laryngoscope* 1985; 95:1220-1223.). The interval to repeat surgery has been selected as the primary outcome measure in this proposed study. By using this continuous outcome measure on our study population with required regular follow up evaluation, both subjective outcomes such as patient symptoms and objective measures such as spirometry measurements and office examination of the airway diameter will be taken into consideration.

Clinical COPD Questionnaire: The Clinical COPD Questionnaire is a 10-item psychophysical scale which was developed for patients with Chronic Obstructive Pulmonary Disease. The questionnaire requires the patients to rate respiratory symptoms, as well as functional and mental limitations related to their breathing. Based on a study of 33 adult LTS patients, the CCQ was found to be valid and sensitive instrument for assessing symptom severity and levels of function and well-being in adult LTS patients (*Nouraei et al.). In the proposed study, the CCQ will be administered to the patients preoperatively and at every scheduled postoperative and subsequent follow up visit.

Pulmonary Function Testing (PFTs): Flow volume loops obtained in pulmonary function testing have long been used in the evaluation of dyspnea to differentiate between fixed and variable lesion and to differentiate between intrathoracic or extrathoracic obstruction. As PFTs are non-invasive and easy to perform in the clinical setting, they provide useful information in the diagnosis and monitoring of LTS patients. Various indices have been proposed as sensitive measures for LTS, including PEF/PIF, MEF50/MIF50, among others (Nouraei et al *Laryngoscope* 2007). In practice, it is difficult to accurately predict the degree of stenosis based on the spirometry results. However, many laryngologists consider a peak inspiratory flow (PIF) of less than 1.5 L per second to indicate a significant level of airway obstruction. The proposed study will improve our understanding of the association between patient symptoms and objective pulmonary function testing measurements.

C. Preliminary Study

C.1 Endoscopic Management of Adult Subglottic Stenosis Patients at the UCSF Voice and Swallowing Center. In 2008, Drs. Roediger, Orloff, and Courey published a retrospective case series review of 15 consecutive adult subglottic stenosis patients

treated over a 3 year period. All patients underwent microdirect subglottoscopy under jet ventilation, CO2 laser radial incisions through the stenotic segment, and topical MMC application in a concentration of 0.5mg/ml for 3 minutes. 28 total procedures were performed. All subjects reported postoperative reduction in symptoms. Six patients (40%) required only one surgical treatment for symptomatic relief during the study period, Nine patients (60%) required repeat surgery at an average interval of nine months²⁰. **Relevance to proposed research:** This works supports endoscopic management with laser radial incisions and topical MMC application as an effective treatment for SGS. Due to the retrospective nature of this study and lack of a control group, the efficacy of the topical MMC application cannot be determined. It is possible that the results are due to the surgical treatment without an additional benefit from the MMC. The proposed study will directly address whether the use of MMC is an effective adjunctive therapy.

C.2 Experience and Expertise in Surgical Treatment of LTS: Presently at the UCSF Voice and Swallowing Center, LTS patients that are candidates for endoscopic surgical management are treated with CO2 laser radial incision, controlled balloon dilation, and given the option of topical MMC application. I have been performing these airway surgeries on my own patients since 2008. Since the completion of my residency training, I have performed XX endoscopic surgeries for the treatment of LTS. All patients without cartilaginous involvement have had at least temporary relief from respiratory symptoms. Most require repeat treatments consistent with the aforementioned published work from our center. **Relevance to proposed research:** I have the necessary expertise and experience to perform the surgical procedures in this study.

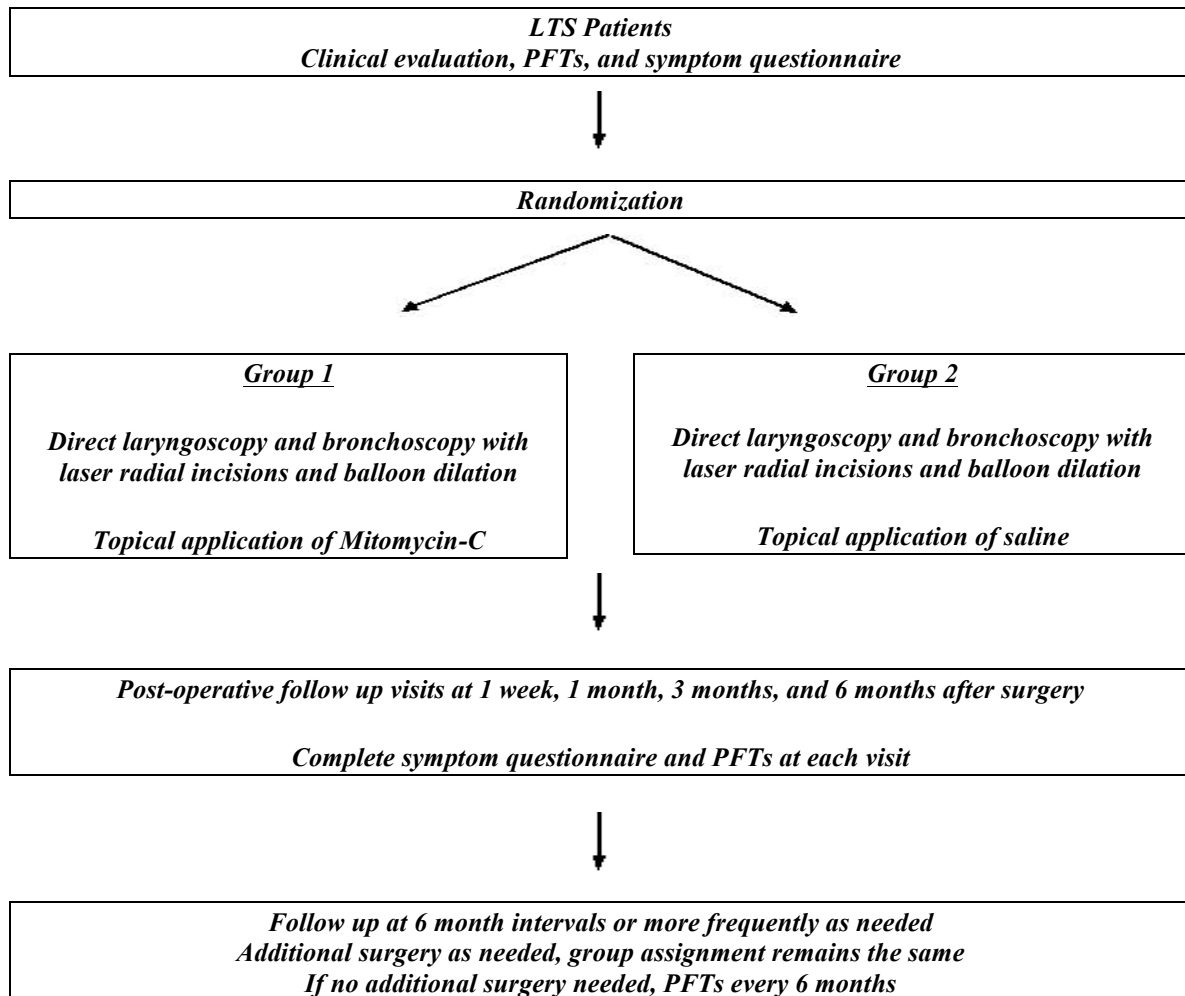
D. Research Design and Methods

D.1 Overview of study design: The overall goal in this study is to evaluate the effect of topical MMC therapy as an adjuvant to endoscopic surgical treatment in LTS patients. We plan to accomplish this by comparing a group of LTS patients who undergo endoscopic surgical management with the addition of MMC against a control group of LTS patients who undergo endoscopic surgical management without MMC in a prospective, placebo-controlled, double-blinded fashion.

After eligibility is determined, LTS patients will undergo a clinical evaluation that includes a history and physical examination including videolaryngoscopy, clinical COPD questionnaire, and pulmonary function testing. Prior to surgery, the patients will be randomized into one of two groups: 1) endoscopic surgical treatment with topical application of saline and 2) endoscopic surgical treatment with topical application of saline. Both the patient and the physician will be blinded to the treatment group assignment. Patients will be evaluated at regular post-operative intervals. Symptom questionnaires and laryngoscopy will be performed at each office visit. PFTs will be performed at 1 month and 6 months post-operatively. Additional surgery will be performed as needed and group assignments will remain the same. After the initial 6

month post-operative period, if patients remain asymptomatic, office visits and PFTs will be performed at 6 month intervals until the completion of the 24 month study period.

Figure 1. Schematic diagram of study



D.2 Study population: Based on our sample size calculation (Section XX), we will enroll 60 subjects with LTS.

Eligibility: Patients with subglottic or tracheal stenosis will be considered for enrollment into the study based on the following:

Inclusion criteria:

- Age greater than or equal to 18 years

- Patients with disease amenable to treatment with endoscopic CO2 laser radial incisions and balloon dilation

Exclusion criteria:

- Minors (age less than 18 years) and pregnant women
- Patients with glottic and supraglottic stenosis
- Patients with disease not amenable to treatment with endoscopic CO2 laser radial incisions and balloon dilation
- Patients with cartilaginous subglottic or tracheal stenosis

D.3 Rationale for study design and study populations: The proposed project is designed to be a prospective, randomized, placebo-controlled, double-blinded study to evaluate the effect of topical MMC as an adjuvant treatment to endoscopic surgical management in LTS. Endoscopic surgical treatment including CO2 laser radial incisions and dilation has been demonstrated to be an effective treatment of LTS. MMC is routinely used as an adjuvant therapy. However, the efficacy of MMC remains questionable. Despite the presence of retrospective studies that have supported the use of MMC, there have been no prospective controlled studies directly addressing the efficacy of MMC in adult LTS patients. Randomization of the patients into a MMC group or a placebo group should not expose them to additional or unnecessary risks, as in both groups the patients will be treated with the surgical standard of care. While the efficacy of MMC is unknown, the safety of topical MMC has been well-accepted. Hueman and Simpson reported 4 complications that were believed to be caused by local toxicity of MMC out of 85 cases⁹. Complications were manifested by the presence of fibrinous debris at the operative site, resulting in airway restriction and need for airway intervention. The complication rate with the standard concentration was 2.8% (2/71), while the complication rate for the supersaturated concentration was 14% (2/14). For this reason, we will use the standard concentration of 0.4mg/ml. Patients return for follow up 1 week and 1 month postoperatively to evaluate for symptomatic and/or laryngoscopic improvement, as well as for adverse events.

The study population is limited to adults LTS patients, excluding supraglottic and glottic level stenosis. Soft tissue subglottic and tracheal stenosis is well treated with radial incisions and dilation, with the procedure being essentially identical for either diagnosis. The presentation and treatment of supraglottic and glottic level stenosis is more varied and direct comparisons between these groups and the more static subglottic/tracheal stenoses would be less reliable. Therefore, to eliminate variation in patient population and surgical treatment, we have decided to limit the study population to adult LTS patients. We have not excluded tracheotomized patients, as the presence or absence of the tracheotomy does not change our treatment of the stenotic region. Patients are treated endoscopically with the intention to decannulate as soon as possible.

D.4 Study procedures

Subject recruitment and informed consent: Patients seen at the UCSF Voice and Swallowing Center who meet the eligibility criteria for this study will be approached by

Drs. Yung or Courey for enrollment. Drs. Yung or Courey will obtain written informed consent for the study

Based on our experience in the past 12 months, we expect to enroll the 60 patients during a 2 year period. Drs. Yung and Courey performed 40 endoscopic CO2 laser radial incisions with dilation in 2011, with similar numbers in the previous years. Accounting for a 25% dropout, this should provide the calculated sample size of 44 subjects.

Baseline visit: Subjects will have a baseline visit from which demographic information, medical history, physical examination including videolaryngoscopy, and the clinical COPD questionnaire will be obtained. This visit will be performed at the UCSF Voice and Swallowing Center. If the patient does not have a previous airway CT scan to document the absence of cartilaginous stenosis, we will obtain one prior to surgery. PFTs will be performed prior to surgery as well.

Surgical procedure: All patients will undergo a uniform surgical treatment. General anesthesia with jet ventilation will be used unless the patient can be ventilated through a tracheotomy. After the induction of general anesthesia, an initial survey of the larynx and pharynx will be performed with a monocular laryngoscope. A subglottoscope will then be inserted into the larynx and suspended. Photodocumentation and measurements of the stenosis will be obtained. The remainder of the surgery is performed with an operating microscope. Using a CO2 laser with a pattern generator, radial incisions will be performed through the stenotic segment. Incisions will be performed to reach the normal lumen of the adjacent trachea or larynx. Using a balloon dilator, the stenotic segment will be dilated to the diameter of the normal tracheal lumen. Cottonoids will be soaked in either MMC in a concentration of 0.4mg/ml or normal saline. These are then applied to the incisions for 3 minutes.

Post-operative visits: Patients will return to the UCSF Voice and Swallowing Center for follow up visits at 1 week, 1 month, 3 months, and 6 months after surgery. At each visit, videolaryngoscopy will be performed and the symptom questionnaire will be completed. PFTs will be obtained at 1 month and 6 months postoperatively. Beyond 6 months, the patients will return for follow up every 6 months or sooner if needed. PFTs will be obtained every 6 months or prior to any additional surgical intervention.

Additional surgery: Patients will undergo additional surgery as their symptoms and stenosis relapse. They remain in their initial randomization for the entire 24 month study period and the surgeries are performed in the manner as described above.

D.5 Study measurements:

Demographics: The patient's age, gender, ethnicity, and race will be recorded.

Medical history: A complete medical history will be obtained from each patient including medical comorbidities, current medications, social history, and family history.

Physical examination: A complete head and neck exam will be performed at each office visit, including videolaryngoscopy.

Interval to repeat surgery: The time interval between the subject's initial surgery and 1st additional surgery will be recorded. Additional intervals will be recorded as needed for all additional surgeries within the study period.

Clinical COPD Questionnaire: The CCQ will be used to assess the patients' respiratory symptoms and their effects on functional status and mood. The total score (continuous variable) will be used as the outcome measure of interest.

Duration of symptom improvement: Symptom improvement will be assessed by comparing pre-operative CCQ scores with the 1st postoperative CCQ score. The duration of symptom improvement will be the duration of time where the improved scores remain stable. The duration of symptom improvement may be a better outcome measure than interval to repeat surgery if a significant number of patients do not need repeat procedures during the study period.

Pulmonary Function Testing (PFTs): Flow volume loops and spirometry measurements will be obtained. Peak inspiratory flow (PIF) will be the main objective measurement used. However, additional data will be recorded for analysis, including PEF, FIV₁, FEV₁, FIVC, FVC, MIF₅₀, MEF₅₀.

D.6 Data quality and data management: Data will be collected by Dr. Yung, Dr. Courey, or their staff during office evaluations. Collected data will be recorded as a hard copy that will then be transferred to an electronic database format. The data will be managed by Wendy Ma, the study coordinator.

D.7 Statistical analysis

Analysis 1: To determine changes seen with topical MMC therapy

Rationale and approach: We hypothesize that the MMC group patients will have longer intervals to repeat surgery than the placebo group, as well as longer durations of symptom improvement when compared to placebo patients. Furthermore, we hypothesize that the two groups will have similar improvements in symptoms and similar improvements in peak inspiratory flow measurements after surgical treatment for LTS. Paired t-tests (within group), t-tests (between groups), and repeated measures techniques (particularly for duration of changes in symptoms) will be used to evaluate outcomes for the mitomycin-c and saline placebo groups.

Analysis 2: To evaluate the association between patients' subjective symptoms and pulmonary function testing measurements.

Rationale and approach: We hypothesize that there will be an association between patient reported symptoms and peak inspiratory flow measures. Linear regression will test the association between patient's subjective symptoms and pulmonary function testing measurements.

Sample size calculation: Sample size determination is based on the primary outcome, the time interval to repeat operation. Analysis of 44 subjects (22 in each arm) would provide 90% power to detect a difference in the time interval to reoperation of 6 months between the two treatment arms, at an alpha level of 0.05. This difference of 6 months is clinically meaningful and is smaller than previous case series studies would suggest. A

sample size of 60 subjects will account for a potential 25% loss to follow up. This sample size should be sufficient for examination of secondary outcomes, based on the limited data that are available.

D.8 Potential problems

We are aware of two potential problems. The interval to repeat surgery was selected as the primary outcome measurement based on the ease of definability and the notion that this outcome measurement would take into account both the patient's symptoms as well as clinical exam findings. However, if a large number of enrolled subjects do not require additional surgery during the 24 month study period, the interval to repeat surgery is a less relevant measure. In that case, a symptom-free interval or duration of symptom improvement may be a better outcome measure. We will collect data on duration of symptom improvement and use this as the primary outcome measure if it appears more appropriate. Although we expect to be able to enroll the necessary number of subjects within our current LTS patients and new referrals, it is possible that study accrual is slow. In this situation, we may decide to publicize our clinical trial in order to recruit more subjects.

D.9 Timeline

ALA Award would represent Year 1.

Activity	Year 1	Year 2	Year 3	Year 4
Enrollment of patients	*	*		
Study assessments	*	*	*	
Data cleaning and statistical analysis			*	*
Manuscript preparation and presentation of results			*	*

E. Human Subjects

E.1 Risks to the subjects

Human subjects involvement and characteristics: The patient sample for this research plan is adult patients with LTS seen in Dr. Yung and Dr. Courey's practices at the UCSF Voice and Swallowing Center. Complete inclusion and exclusion criteria are outlined in Study Population, Section D.2.

Sources of materials: Research material will be obtained from direct assessment of the patient, including medical history, physical examination, PFTs, and CCQ.

Potential risks: The risks of physical examination including videolaryngoscopy are negligible. The risks of pulmonary function testing are also negligible. There have been few reported adverse events with topical MMC application. In humans, multiple studies also document the absence of adverse effects with topical mitomycin. The standard

dosage of 0.4mg/ml was used in most studies, with one author also including a 10mg/ml supersaturated concentration. Only 2 studies in the otolaryngology literature note possible complications from topical MMC use. Ubell et al. published a series of 50 patients who underwent 93 MMC applications. Only 1 suspected complication occurred in a patient with recurrent laryngeal amyloidosis who reported throat pain and dyspnea two weeks postoperatively. Diffuse laryngeal inflammation was noted and the patient ultimately required a tracheotomy. Although it is unclear whether MMC was directly responsible for this adverse event, the authors considered it a complication resulting in a complication rate of 1.1%. Hueman and Simpson reported 4 complications that were believed to be caused by local toxicity of MMC out of 85 cases. Complications were manifested by the presence of fibrinous debris at the operative site, resulting in airway restriction and need for airway intervention. The complication rate with the standard concentration was 2.8% (2/71), while the complication rate for the supersaturated concentration was 14% (2/14). For this reason, we will use the standard concentration of 0.4mg/ml. Patients return for follow up 1 week and 1 month postoperatively to evaluate for symptomatic and/or laryngoscopic improvement, as well as for adverse events.

Additional risks of this study include the risk of randomization and the risk of radiation from the CT scan that is done as part of the pre-treatment/enrollment evaluation. As an effect of the study randomization, subjects in one arm of the study, whether it is the MMC arm or the placebo arm, may have more side effects or receive treatment that may prove to be less effective than the other arm. The amount of radiation the subject is exposed to in a non-contrast neck CT scan is relatively small, but the risk of potential future harm can not be determined.

E.2 Adequacy of protection against risks

Recruitment and informed consent: Recruitment will not influence any treatment decisions. Patients with LTS will be approached by either Dr. Yung or Dr. Courey regarding the study only after the decision to proceed with surgical treatment has been made. Patients who decide not to enroll in the study will be offered standard LTS treatment and given the option of topical MMC. Informed consent will be obtained by either Dr. Yung or Dr. Courey, although certain aspects of the study may be explained in greater detail by Wendy Ma, the study coordinator. Emphasis will be placed on the independence of consent for this study and their surgical treatment, the ability to undergo treatment outside the study and that participation in the study will not affect their office evaluation and treatment. Patients will receive a copy of the consent form and the Experimental Subject's Bill of Rights.

Protection against risk: Study patients will undergo topical application of MMC at the same concentration and the same application time as non-study patients. The standard concentration of 0.4mg/ml will be used. Their airway symptoms will be monitored with close office follow up evaluations at one week and one month post-operatively. Patients will notify the UCSF Voice and Swallowing Center nursing staff or otolaryngologist of any adverse side effects they are experiencing. Essentially, the symptom questionnaire is the only study component that standard non-study LTS patients do not undergo and as

such, there is little if any additional risk that subjects will experience by agreeing to take part in this study. In order to protect the privacy of research subjects, study personnel will follow all HIPAA regulations and maintain data on password-protected computers and/or secure networks. Privacy in the research setting will include meeting in a private room for the consent discussion, conducting all office visits in a private examination room, using study ID numbers instead of names on data collection forms, storing all identifiers separately and securely from study data, and restricting access to research records.

E.3 Potential benefits of the proposed research to the subjects and others

The proposed study will be the first randomized, prospective, double-blind, placebo controlled clinical trial of MMC as an adjunctive therapy to endoscopic surgical treatment in adult patients with LTS. If this study shows that topical MMC therapy reduces the frequency of repeated airway surgeries for patient with LTS, society would benefit in terms of health care cost and resources. If this study shows that topical MMC therapy has no effect on the frequency of repeated surgeries, then future patients would not be offered MMC, therefore eliminating the cost of the medication as well as any potential adverse effects from the MMC. In either instance, this study should advance our knowledge in the field, provide information regarding the use of MMC in LTS patients, and lead to improved treatment.

12.3

1. Goldenberg D, Esclamado R, Flint P, Cummings CW. Surgical management of upper airway stenosis. In: Cummings CW, Flint PW, Harker LA, Haughey BH, Richardson MA, Robbins KT, Schuller DE, Thomas JR, eds. *Cummings Otolaryngology Head & Neck Surgery*. Philadelphia, PA: Elsevier Mosby; 2005:2103-2127.
2. Simpson GT, Strong MS, Healy GB, Shapshay SM, Vaughan CW. Predictive factors of success or failure in the endoscopic management of laryngeal and tracheal stenosis. *Ann Otol Rhinol Laryngol*. 1982; 91:384-388.
3. Supance JS. Antibiotics and steroids in the treatment of acquired subglottic stenosis. A canine model study. *Ann Otol Rhinol Laryngol* 1983; 92:377-382.
4. Croft CB, Zub K, Borowiecki B. Therapy of iatrogenic subglottic stenosis: a steroid/antibiotic regimen. *Laryngoscope* 1979; 89:482-489.
5. Cobb WB, Sudderth JF. Intralesional steroids in laryngeal stenosis. A preliminary report. *Arch Otolaryngol* 1972; 96:52-56.
6. Hata T, Sano Y, Sugawara R, et al. Mitomycin, a new antibiotic from streptomyces. *Int J Antibiot* 1956; 9:141-146.
7. Tomasz M, Palom Y. The mitomycin bioreductive antitumor agents: cross-linking and alkylation of DNA as the molecular basis of their activity. *Pharmacol Ther* 1997; 76:73-87.

8. Yamamoto T, Varani J, Soong HK, Lichter PR. Effects of 5-fluorouracil and mitomycin C on cultured rabbit subconjunctival fibroblasts. *Ophthalmology* 1990; 97:1204-1210.
9. Kunitimo N, Mori S. Studies on the pterygium. Part IV. A treatment of the pterygium by mitomycin-C instillation. *Acta Soc Ophthalmol* 1963; 67:610-617.
10. Ward RF, April MM. Mitomycin-C in the treatment of tracheal cicatrix after tracheal reconstruction. *Int J Pediatr Otorhinolaryngol* 1998; 44:221-226.
11. Eliashar R, Gross M, Maly B, Sichel JY. Mitomycin does not prevent laryngotracheal repeat stenosis after endoscopic dilation surgery: an animal study. *Laryngoscope* 2004; 114:743-746.
12. Shvidler J, Bothwell NE, Cable B. Refining indications for the use of mitomycin C using a randomized controlled trial with an animal model. *Otolaryngol Head Neck Surg* 2007; 136:653-657.
13. Rahbar R, Valdez TA, Shapshay SM. Preliminary results of intraoperative mitomycin-C in the treatment and prevention of glottic and subglottic stenosis. *J Voice* 2000; 14:282-286.
14. Hirshoren N, Eliashar R. Wound-healing modulation in upper airway stenosis- myths and facts. *Head Neck* 2009; 31:111-126.
15. Perepelitsyn I, Shapshay SM. Endoscopic treatment of laryngeal and tracheal stenosis- has mitomycin C improved outcome? *Otolaryngol Head Neck Surg* 2004; 131:16-20.
16. Simpson CB, James JC. The efficacy of mitomycin-C in the treatment of laryngotracheal stenosis. *Laryngoscope* 2006; 116:1923-1925.
17. Hartnick CJ, Hartley BE, Lacy PD, et al. Topical mitomycin application after laryngotracheal reconstruction: a randomized, double-blind, placebo-controlled trial. *Arch Otolaryngol Head Neck Surg* 2001; 127:1260-1264.
18. Smith ME, Elstad M. Mitomycin C and the endoscopic treatment of laryngotracheal stenosis: are two applications better than one? *Laryngoscope* 2009; 119:272-283.
19. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; 138:700-709.
20. Roediger FC, Orloff LA, Courey MS. Adult Subglottic Stenosis: Management with laser incision and mitomycin-C. *Laryngoscope* 2008; 118:1542-1546.